Cracking the Genetics of Disease

We are all created equal. Or perhaps 99.99 percent equal, at least genetically speaking. The other 0.01 percent variation is what can make the difference between health and disease. Scientists at the Broad Institute, an MIT-Harvard collaboration, are stepping up their analyses to identify the genetic variations that determine our susceptibility to common disorders such as heart attack, diabetes, autoimmune diseases, and hypertension. The emphasis on common disorders and study of multiple genetic variations marks an advance from the 1990s, when single genes that cause severe disease, such as cystic fibrosis, were first identified.

Now, scientists can compare the vast majority of genetic variation carried in sequences of healthy and ill individuals. In practice this approach, called whole-genome genotyping, is feasible for the first time ever. The process identifies the genotype at hundreds of thousands of positions across the genome. "There is tremendous advantage in terms of cost and efficiency to using these whole genome genotyping approaches," says geneticist Stacey Gabriel, director of the Center for Genotyping and Analysis at the Broad Institute. In contrast, attempting to compare complete DNA sequences between individuals would be entirely cost prohibitive. Comparing one gene at a time for variations also would be a slow process, considering that humans have 30,000 genes. To further complicate matters, susceptibility to most common diseases is determined by a multitude of genes. Identifying the best treatment for common diseases will likely require knowledge of the predisposing genes.

To increase the availability of genotyping for medical researchers, NCRR awarded a five-year, $14 million grant to develop the Center for Genotyping and Analysis in 2004. "The Broad Institute is clearly a leader in genotyping analysis because of their previous experience with other large-scale projects that have analyzed variation in the human genome," says Anthony Hayward, director of NCRR's Division for Clinical Research Resources.

The center has developed a strategic approach by looking only at the most common type of mutation in the genome, the single nucleotide polymorphism (SNP), or "snip." A SNP is the mutation of a single DNA base (A, T, C, or G) along the genome.

Stacey Gabriel and her team at the Broad Institute collaborate with disease consortia for multiple sclerosis, lupus, and type 1 diabetes to determine links between genetics and disease.

In essence, SNPs are genetic markers that crop up roughly every 300 bases. SNPs need to be thought of as the genetic basis for our individuality—not so much "mutations" as the variability that makes each of us unique. However, certain combinations of SNPs predispose individuals to disease. Scientists estimate that there are 10 million locations where SNPs can occur.

At the Center for Genotyping and Analysis, scientists are examining SNPs in hundreds of thousands of different combinations along the genome. To accomplish this effectively, the center utilizes state-of-the-art technology, including gene chips that can map, or genotype, up to 500,000 SNPs at a time in predetermined genome sections.

Preliminary results of these scans help researchers decide if they should look more closely at selected genes or move on and analyze another combination of SNPs. The idea is to cast a wide net and then focus in on specific SNP combinations. By using targeted genotyping, researchers can develop comparisons between healthy and diseased populations more rapidly and cost-effectively.

Currently, the center is working with several consortia—focusing on multiple sclerosis, lupus, type 1 diabetes, cancer and bipolar disorder—to examine thousands of genetic samples for each disease. "These studies will wrap up in the next two years," says Gabriel. "What we will know about these diseases two years from now will be totally changed." Understanding gene mutations also may help to develop new drugs and diagnostic strategies for the future.

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Researchers can now take advantage of the laboratory's facilities to genotype their samples at a reduced cost through a new program that accepts applications twice yearly. "We offer the ability to manage and analyze data for whole-genome scans, which are in great demand and currently predominate in our work," says Gabriel. Interested scientists can submit their human or animal DNA for SNP analysis. "It has been great to be selected by NCRR to help other people do the kinds of studies that we're already doing. It's really about leveraging what is already there," Gabriel adds. **—AL STAROPOLI**

TO GAIN ACCESS: Researchers can apply for subsidized genotyping by filling out an application found on the Center for Genotyping and Analysis Web site at www.broad.mit.edu/genotyping/upload.html. Applications are accepted twice yearly. The next round of applications is due in June 2006.

A Measure of Age

Don Ingram pinches the skin on his forearm and wonders what happened to its elasticity. Now in his 50s, he has studied aging at the National Institute on Aging for nearly 30 years. "I'm now hitting full stride in my productive adult life. Why is it that we must lose that vigor?" says Ingram. Interestingly enough, some people reach their 60s in very poor physical and mental condition, while others in their 80s are still healthy and clearheaded. This is because chronological age is not the same as biological age. Scientists believe that biological changes in the body, rather than years of life, could be better predictors of health and potential life span. These changes can be measured through biomarkers such as glucose, blood cell count, cholesterol, and insulin.

Biological data gathered over decades from older primates, like the one shown here, could help researchers better understand the aging process in humans.

The National Institute on Aging and the NCRR-funded Wisconsin National Primate Research Center (NPRC) have announced the debut of an online biomarker database for aging research, the Internet Primate Aging Database, or iPAD. The iPAD contains tens of thousands of biomarker data such as cholesterol, body weight, hemoglobin, and 33 others, collected over the life spans of numerous primates. "Each of these biomarkers may affect aging in a different way," says Wendy Newton, research specialist at the NPRC. Understanding how biomarkers function may help explain the connection between biology and aging, she adds. The iPAD has already spurred several papers published in peer-reviewed journals.

Using data retrieved from iPAD, Ingram and colleagues examined various biomarkers in an aging population of 345 healthy rhesus monkeys. Their study concluded that age does indeed influence biomarkers. In particular, lymphocytes, white blood cells that identify and attack viruses, showed a marked change. "Just when we begin needing them as we get older, their numbers go down," says Ingram. By monitoring biomarkers in primates, which generally have much shorter life spans than humans, scientists can evalaute whether interventions such as exercise, diet, hormones, pharmaceuticals, or dietary additives can slow the rate of aging.

The iPAD allows researchers to perform detailed data queries by gender, age, site, diet type, primate species, or a specific biomarker. Statistical query results can be downloaded into a spreadsheet for further manipulation or presented in table form along with mean, standard deviation, standard error, and total number of data points. This powerful database will soon incorporate graphing functions and other add-ons. Previously available only on CD-ROM, the database is now available to researchers, free of charge, on the Web.

"Because the aging process is remarkably similar in humans and nonhuman primates," says Ingram, "clinical investigators could benefit from a preliminary analysis of iPAD data before developing human studies." This could provide scientists with valuable insights as they begin to establish protocols for aging research. **—AL STAROPOLI**

TO GAIN ACCESS: The iPAD is supported by the National Institute on Aging and the Wisconsin National Primate Research Center, one of eight NCRR-funded primate research centers nationwide. To access iPAD, request a user name and password at http://iPAD.primate.wisc.edu. With more than 500,000 data points from 17 different nonhuman primate species, users can view biomarker data that spans an animal's lifetime. Researchers interested in becoming part of this interdisciplinary, collaborative effort can contribute their primate data by contacting the iPAD system administrator, Wendy Newton, at wnewton@primate.wisc.edu.

PHOTO BY J. LENON, WISCONSIN NATIONAL PRIMATE RESEARCH CENTER